

Null Results in Brief

Medication Use, Medical Conditions, and the Risk of Human Papillomavirus Infection and Subsequent Cervical Intraepithelial Neoplasia 3 Among Women with Mild Cytologic Abnormalities

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Introduction

Although profound immunosuppression by such factors as HIV infection and organ transplantation are associated with human papillomavirus (HPV) infection and cervical neoplasia (1), it remains unclear whether mild immune perturbation from medication use or from medical conditions such as asthma, allergies, and depression, would also alter risk for HPV status and cervical cancer. It also remains unclear whether use of pain medication (e.g., nonsteroidal anti-inflammatory drugs or NSAID), which has been suggested to decrease risk for other tumors (e.g., prostate and colon; refs. 2-4), does so for the cervix. The goal of the present manuscript is to explore associations between medical conditions/medications and HPV infection and, among women infected with HPV, to determine whether risks were altered for developing cervical precancers.

Materials and Methods

Study Population. The study design and characteristics of the ASCUS LSIL Triage Study (ALTS) have previously been described (5, 6). Briefly, 5,060 women (3,488 with atypical squamous cells of undetermined significance and 1,572 with low-grade squamous intraepithelial lesion diagnosed by cytology) were enrolled in the study from January 1997 to December 1998 at four clinical sites (University of Alabama at Birmingham, Birmingham, AL; Magee-Women's Hospital, Pittsburgh, PA; University of Oklahoma Health Sciences Center, Oklahoma City, OK; and University of Washington, Seattle, WA). Women were invited for follow-up visits every 6 months with a final exit visit conducted after 2 years.

Questionnaire Data. At enrollment, a detailed study questionnaire was given as previously described (7). Participants were asked whether they had any major health problems for which they were being observed or for which medication was taken regularly. If so, they were asked to

define their health condition and indicate medication use by category or name; all responses were comprehensively reviewed and resulted in the following medication categories: analgesics, antibiotics, antidepressants, immunosuppressives (including corticosteroids), antiasthmatics, and NSAIDs. Medical conditions reported included asthma, depression, allergies, diabetes, headaches, and autoimmune conditions.

HPV DNA Testing. As previously reported (7, 8), testing by hybrid capture 2 (HC2, Digene Corporation, Gaithersburg, MD) for 13 oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) was conducted using residual PreservCyt (Cytoc Corporation, Boxborough, MA) cytology aliquots collected at enrollment. HPV testing using L1 consensus primer PGM09/11 PCR amplification and reverse-line blot hybridization for type-specific detection (9) was also conducted on cervical specimens collected in specimen transport medium (Digene). Briefly, reverse line blotting using HPV genotyping strips (Roche Molecular Systems, Alameda, CA) was used to detect 27 HPV genotypes [6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51-55, 56-59, 66, 68, 73 (PAP238A), 82 (W13B), 83 (PAP291), and 84 (PAP155)] and a β -globin internal control.

Oncogenic HPV-positive women were defined as women positive by HC2 or by PCR for the targeted 13 oncogenic types. Women who tested negative for oncogenic types with HC2, but were positive for other types not included in the HC2 kit were considered to have nononcogenic HPV infections. Women who tested positive with HC2 but were PCR-negative for the 13 oncogenic types included in the HC2 kit and positive for HPV 6, 53, 66, 67, or 81 were considered to have nononcogenic infections because of known HC2 cross-reactivity (10). HPV-negative women had no detectable HPV types, by either assay.

Pathology Outcome. The histologic end point of interest was defined as precancer, i.e., cervical intraepithelial neoplasia 3, or cancer (\geq CIN3) diagnosed either at enrollment or during the 2-year follow-up by an expert pathology review group (5, 7). We also included CIN2 as an end point of clinical interest.

Statistical Analyses. Among women with valid HPV results at enrollment and who did not develop CIN2 or worse during follow up ($n = 4,114$), we calculated crude and age-adjusted odds ratios (OR) and 95% confidence intervals (CI), using SAS version 8.2 (SAS Institute, Inc., Cary, NC) to assess the associations between medical condition and medication use with HPV status (2,266 oncogenic HPV, 504 nononcogenic HPV, and 1,344 HPV-negative women). To assess possible cofactors for progression among women with oncogenic HPV infections ($n = 3,133$), we calculated crude and age-adjusted OR and 95%

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CI were for developing CIN2 ($n = 361$) and \geq CIN3 ($n = 506$), considering women with oncogenic HPV infections who did not develop CIN2 or worse as the referent ($n = 2,266$).

Results

Medication use and medical conditions were uncommon, but correlated as expected: 91% of women with asthma reported use of antiasthma medication, 75% of women with anxiety or depression reported antidepressant use, 69% of women with allergies also reported use of allergy medication, and 63% of women reporting headaches and migraines noted the use of analgesics/painkillers. Use of antidepressants were most common (6-7%).

The use of analgesics or NSAIDs decreased a woman's risk for testing positive for an oncogenic HPV type (OR, 0.6; 95% CI, 0.4-1.0), albeit not statistically significantly (Table 1). However, this decrease in risk was not observed for non-oncogenic HPV infections or for overall HPV detection (any type). None of the medical conditions associated was associated with HPV detection. No medications were associated with consistently altered disease risk among women infected with oncogenic HPV types. Women reporting depression had increased risk for CIN2 but not CIN3 or worse diagnosis (OR, 1.9; 95% CI, 1.1-3.1); similarly, the risk of CIN2 was increased for women reporting headaches, but this was not observed for \geq CIN3 (Table 2).

Discussion

The ALTS population is a useful cohort for studying HPV cofactors among a large group of young women who were carefully followed with serial HPV testing and cytologic assessment (11). We did not find statistically significant

associations between self-reported medical conditions or medication use with HPV status, nor with CIN2 or greater disease among women infected with oncogenic HPV types. Although there seemed to be a protective association between NSAID or analgesic use and oncogenic HPV status, this was not statistically significant and there was no further association with disease status among women who tested positive for non-oncogenic HPV. Only weak associations were observed between medical conditions (e.g., headaches and depression) and CIN2 (which is usually treated but regresses spontaneously); associations for the more certain cancer precursor, CIN3, were null.

Study strengths include the large population size and rigorous HPV testing and pathologic classification. Although there was sufficient power for HPV outcomes, the low prevalence of our exposures did limit power for cervix outcomes, although we did find some marginally statistically significant associations. We adjusted all analyses by age, but additional adjustment was not possible secondary to low exposure prevalence. Although limitations to the current analysis include the lack of duration or dose data for medication use and severity of medical conditions, a strength was the ability to assess the exposures concurrent with HPV detection. In addition, only medical conditions that required physician's attention were reported, and moderate/intermittent medication usage was not likely to have been reported. Although a strong association would have been observed had it existed, we nevertheless cannot exclude misclassification of exposure as a reason for our null result. ALTS included young women with limited 2-year follow-up and we therefore cannot generalize our findings to older women.

We conclude that self-reported medication use and medical conditions are not likely to be strongly associated with HPV infection or with developing subsequent CIN3. Based on a previous report (12), however, supported somewhat by our finding for depression and CIN2, further studies may be

Table 1. Medication use, medical conditions, and age-adjusted risk for HPV infection among women with mild cytologic abnormalities but not developing CIN2 or greater outcomes during 2-year study

		HPV-negative ($n = 1,344$)		Nononcogenic HPV + ($n = 504$)		Oncogenic HPV + ($n = 2,266$)*	
		n (%)		n (%)	Age-adjusted OR (95% CI)	n (%)	Age-adjusted OR (95% CI)
<i>Medications</i>							
Antiasthma	No	1,304 (97)		490 (97)		2,204 (97)	
	Yes	40 (3)		14 (3)	1.1 (0.6-2.1)	60 (3)	1.1 (0.7-1.7)
Allergy	No	1,321 (98)		500 (99)		2,251 (99)	
	Yes	23 (2)		4 (1)	0.7 (0.2-2.1)	13 (1)	0.5 (0.2-1.1)
Antidepressants	No	1,261 (94)		483 (96)		2,191 (97)	
	Yes	83 (6)		21 (4)	1.0 (0.6-1.6)	73 (3)	0.9 (0.6-1.2)
Antihypertensive	No	1,291 (96)		489 (97)		2,232 (99)	
	Yes	53 (4)		15 (3)	1.5 (0.8-2.7)	32 (1)	1.2 (0.8-2.0)
NSAIDs/analgesics	No	1,283 (95)		484 (96)		2,228 (98)	
	Yes	61 (5)		20 (4)	1.3 (0.8-2.2)	36 (2)	0.6 (0.4-1.0)
Antibiotics	No	1,337 (99)		501 (99)		2,246 (99)	
	Yes	7 (1)		3 (1)	0.9 (0.2-3.5)	18 (1)	0.9 (0.4-2.2)
Immunosuppression	No	1,332 (99)		503 (100)		2,261 (100)	
	Yes	12 (1)		1 (0)	1.4 (0.1-13.6)	3 (0)	1.4 (0.3-7.5)
<i>Medical conditions</i>							
Asthma	No	1,300 (97)		489 (97)		2,207 (97)	
	Yes	44 (3)		15 (3)	1.1 (0.6-2.0)	57 (3)	0.9 (0.6-1.4)
Allergies	No	1,318 (98)		499 (99)		2,243 (99)	
	Yes	26 (2)		5 (1)	0.7 (0.3-1.9)	21 (1)	0.7 (0.4-1.4)
Depression	No	1,254 (93)		474 (94)		2,190 (97)	
	Yes	90 (7)		30 (6)	1.3 (0.8-2.0)	74 (3)	0.8 (0.5-1.1)
Diabetes	No	1,318 (98)		493 (98)		2,239 (99)	
	Yes	26 (2)		11 (2)	1.9 (0.9-4.0)	25 (1)	1.3 (0.7-2.3)
Headaches	No	1,326 (99)		494 (98)		2,249 (99)	
	Yes	18 (1)		10 (2)	2.0 (0.9-4.5)	15 (1)	0.7 (0.3-1.6)
Autoimmune	No	1,332 (99)		499 (99)		2,246 (99)	
	Yes	12 (1)		5 (1)	1.4 (0.5-4.2)	18 (1)	1.5 (0.7-3.4)

*Totals do not add up to due to missing values.

Table 2. Medication use, medical conditions among oncogenic HPV-positive women, and risk for CIN2 and ≥CIN3 during the 2-year study

		<CIN2 (<i>n</i> = 2,266)*		CIN2 (<i>n</i> = 361)		≥CIN3 (<i>n</i> = 506)	
		<i>n</i> (%)		<i>n</i> (%)	Age-adjusted OR (95% CI)	<i>n</i> (%)	Age-adjusted OR (95% CI)
<i>Medications</i>							
Asthma	No	2,204 (97)		357 (99)		496 (98)	
	Yes	60 (3)		4 (1)	0.4 (0.1-1.1)	10 (2)	0.8 (0.4-1.5)
Allergy	No	2,251 (99)		358 (99)		504 (100)	
	Yes	13 (1)		3 (1)	1.6 (0.4-5.5)	2 (0)	0.7 (0.2-3.3)
Antidepressants	No	2,191 (97)		348 (96)		497 (98)	
	Yes	73 (3)		13 (4)	1.1 (0.6-2.1)	9 (2)	0.6 (0.3-1.1)
Antihypertensive	No	2,232 (99)		359 (99)		502 (99)	
	Yes	32 (1)		2 (1)	0.4 (0.1-1.5)	4 (1)	0.7 (0.2-2.0)
NSAIDs/analgesics	No	2,228 (98)		351 (97)		499 (99)	
	Yes	36 (2)		10 (3)	1.8 (0.9-3.7)	7 (1)	0.9 (0.4-2.1)
Immunosuppressants	No	2,261 (100)		361 (100)		506 (100)	
	Yes	3 (0)		0 (0)	NA	0 (0)	NA
<i>Medical conditions</i>							
Asthma	No	2,207 (97)		356 (99)		497 (98)	
	Yes	57 (3)		5 (1)	0.5 (0.2-1.4)	9 (2)	0.7 (0.3-1.4)
Allergies	No	2,243 (99)		358 (99)		506 (100)	
	Yes	21 (1)		3 (1)	0.9 (0.3-3.1)	0 (0)	NA
Depression	No	2,190 (97)		340 (94)		494 (98)	
	Yes	74 (3)		21 (6)	1.9 (1.1-3.1)	12 (2)	0.7 (0.4-1.4)
Diabetes	No	2,239 (99)		359 (99)		504 (100)	
	Yes	25 (1)		2 (1)	0.5 (0.1-2.2)	2 (0)	0.4 (0.1-1.7)
Headaches	No	2,249 (99)		355 (98)		502 (99)	
	Yes	15 (1)		6 (2)	2.5 (1.0-6.6)	4 (1)	1.2 (0.4-3.8)
Autoimmune	No	2,246 (99)		360 (100)		501 (99)	
	Yes	18 (1)		1 (0)	0.4 (0.1-2.6)	5 (1)	1.3 (0.5-3.6)

*Totals do not add up to due to missing values.

warranted on psychosocial stress indicators and cervical neoplasia, with more detailed information on medication use and exposure indicators, preferably with longitudinal data on HPV clearance, persistence, and progression.

Appendix A. Affiliations of the ALTS Group

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